PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
BAXTER HEALTHCARE CORPORATION
Attn. Guthrie, Janice
P.O. Box 15210
Irvine, CA 92623-5210
UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference NV-1939	Date of mailing *(day/month/year)* 09/12/2004
International application No. PCT/US2004/020048	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant BAXTER INTERNATIONAL INC.	International filing date *(day/month/year)* 23/06/2004

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Wolfgang-Peter Schießl

Form PCT/ISA/220 (January 2004) *(See notes on accompanying sheet)*

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/020048	23.06.2004	23.06.2003

International Patent Classification (IPC) or both national classification and IPC
A61K39/385, A61K39/095, A61K39/40, A61K47/48, C07H1/00

Applicant
BAXTER INTERNATIONAL INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Jenn, T

Telephone No. +49 89 2399-7348

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/020048

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☑ claims Nos. 23

because:

☑ the said international application, or the said claims Nos. 23 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23,27,28
	No:	Claims	24-26
Inventive step (IS)	Yes:	Claims	none
	No:	Claims	1-28
Industrial applicability (IA)	Yes:	Claims	1-22,24-28
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.

PCT/US2004/020048

Re Item I

Basis of the report

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Reference is made to the following documents:

D1: BHATTACHARJEE A K et al.: "Structural Determination of the Polysaccharide Antigens of *Neisseria-meningitidis* Serogroup Y, Serogroup W-135 and Serogroup BO" CANADIAN JOURNAL OF BIOCHEMISTRY, vol. 54, no. 1, January 1976, pages 1-8, XP009040472 ISSN: 0008-4018, **cited** in the application;

D2: JONES C et al.: "Use and validation of NMR assays for the identity and O-acetyl content of capsular polysaccharides from *Neisseria meningitidis* used in vaccine manufacture." JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS, vol. 30, no. 4, 7 November 2002, pages 1233-1247, XP002307110 ISSN: 0731-7085

D3: WO 00/10599 A (NORTH AMERICAN VACCINE INC) 2 March 2000;

D4: HRONOWSKI L et al.: "E-75: Structure activity studies on *Neisseria meningitidis* group C polysaccharide-protein conjugate vaccines: The effect of O-acetylation on the nature of the antibody response" ABSTRACTS OF THE GENERAL MEETING OF THE AMERICAN SOCIETY FOR MICROBIOLOGY, vol. 93, 1993, page 155, XP009040462 & 93RD GENERAL MEETING OF THE AMERICAN SOCIETY FOR MICROBIOLOGY; ATLANTA, GEORGIA, USA; MAY 16-20, 1993 ISSN: 1060-2011;

D5: WO 94/05325 A (NORTH AMERICAN VACCINE INC) 17 March 1994;

D6: FARLEY E K et al.: "G-1647: Preclinical studies on the development of an optimal meningococcal CYW conjugate vaccine." ABSTRACTS OF THE INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 43, 2003, page 293, XP001203789 & 43RD ANNUAL INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY; CHICAGO, IL, USA; SEPTEMBER 14-17, 2003;

D7: FARLEY E K et al.: "G-1558: Effect of O-acetylation of *Neisseria meningitidis* serogroup Y capsular polysaccharide on development of functional antibodies." ABSTRACTS OF THE INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 43, 2003, page 292, XP001183793 & 43RD ANNUAL INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY; CHICAGO, IL, USA; SEPTEMBER 14-17, 2003.

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Re Item II
Priority

No check has been made as to whether the priority of the application is valid. In the case of the priority not being allowable, documents **D6** and **D7** would constitute prior art within the meaning of Rule 64.1(a) to be considered for Articles 33(2) and 33(3) PCT:

Document **D6** discloses (the references in parentheses applying to this document), a meningococcal conjugate combination which includes serogroups C, Y and W-135: Optimization of the MenCYW formulation was centred on the choice of the carrier protein (tetanus toxoid (TT)) for each serogroup polysaccharide, the O-acetylation status (fully de-O-acetylated for optimal antibody potency) and the size of the polysaccharides prior to their coupling to the carrier protein (abstract).

Document **D7** discloses (the references in parentheses applying to this document), the preparation of Tetanus toxoid (TT) conjugates of dOA (de-O-acetylated) and OA GYMP. The antibodies induced with the dOA GYMP conjugates were able to kill both OA and dOA GYM strains. Further, inhibition of SBA with PS showed dOA GYMP to be significantly more effective than its OA counterpart at inhibiting the SBA of OA bacteria, making the dOA form of the GYMP a better candidate than the OA for vaccine development (abstract).

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The method as claimed in **claim 23** relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT (method of treatment (cf. "administering") carried out on the living human or animal body). Consequently, no opinion will be formulated on the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT, see also the PCT-guidelines IV-2.4.(d) and IV-2.5); an opinion on novelty and inventive step will be given for the alleged effects of a vaccine of claim 11 in the method of claim 23.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. **Novelty**:

1.1 Document **D1** discloses (the references in parentheses applying to this document), acid methanolysis of the serogroup Y meningococcal polysaccharide of *N meningitidis* (Abstract, page 2, right-hand column, § 4), and the de-O-acetylation of said serogroup Y polysaccharide using 0.1 M NaOH (page 2, left-hand column, § 2). This document discloses as well re-N-acetylation of said polysaccharides (page 2, right-hand column, § 4 and 5)
Thus **D1** anticipates the subject-matter of claims 24-26 of the application.

1.2 Document **D2** discloses (the references in parentheses applying to this document), the base-catalysed (using 200 mM NaOH or NaOD) de-O-acetylation of the Group Y capsular polysaccharides from *N. meningitidis* (Abstract, page 1237, § 3.2; Fig 3; page 1242, § 3.6 and 3.7).
Thus **D2** anticipates the subject-matter of claim 25 of the application.

1.3 Therefore, the subject-matter of **claims 24-26** cannot be considered **new** (Article 33(2) PCT).

1.4 The subject-matter of **claims 1-23, 27 and 28** is not anticipated by the available prior art documents, it can therefore be considered **new** (Article 33(2) PCT).

2. **Inventive step**:

2.1 The subject-matter of **claims 24-26** is not new (see above), it can therefore **not** be considered as involving an **inventive** step (Article 33(3) PCT).

2.2 Document **D3** is regarded as being the closest prior art to the subject-matter of independent claims 1, 6, 11, 18-23, 27 and 28, and discloses (the references in parentheses applying to this document), a polysaccharide-protein conjugate comprising an N-propionated polysaccharide (derived from a Meningococcus group selected from the group consisting of group Y, group C, group W135, and combinations there-

of: Claim 6) directly conjugated to a protein (tetanus toxoid, diphtheria toxoid e.g.: Claim 8) at the B-position of the propionate moiety (Claim 1); a vaccine comprising it (Claim 37); and a method of immunizing a mammal comprising administering said vaccine (Claim 41). The polysaccharide is de-N-acetylated by base hydrolysis (Claims 30, 31; page 6, lines 29-33; page 7, line 24 to page 8, line 10), using *e.g.* 2N NaOH (page 17, line 27; page 19, line 16), and re-N-acylated (page 8, line 24 to page 9, line 7). The vaccine can comprise an adjuvant such as aluminum hydroxide (page 13, lines 15-18), and is adapted for administration by injection (page 13, l. 15; page 25, l. 21).

2.2.1 The subject-matter of claims 1, 6, 11, 18-23, 27 and 28 therefore **differs** from this known conjugate/vaccine/use/process in that the group Y meningococccal polysaccharide is de-O-acetylated.

2.2.2 The **problem** to be solved by the present invention may therefore be regarded as to provide an alternative immunogenic conjugate for use against *N. meningitidis* infection.

2.2.3 The **solution** proposed in claims 1, 6, 11, 18-23, 27 and 28 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

Document **D4** discloses (the references in parentheses applying to this document), an immunogenic conjugate of *N. meningitidis* group C polysaccharide coupled to the Tetanus toxoid protein carrier, and its use as vaccine. This document teaches that if the polysaccharide is de-O-acetylated, the quality of the immune response shifts such that superior levels of bactericidal antibodies are obtained when the vaccine is tested in mice.

Document **D5** discloses (the references in parentheses applying to this document), an immunogenic conjugate comprising a (fragmented) de-O-acetylated group C meningococcal polysaccharide in which at least 80% of the 7- and 8-groups of the sialic residues are hydroxyl groups or a fragment thereof, covalently coupled to a suitable carrier material or molecule (tetanus toxoid, pertussis toxin e.g.) (Claims 1-10, 16), and a vaccine comprising said conjugate (claim 19). Document **D5** discloses as well a method of immunizing mammals against *N. meningitides* infection, comprising the step of administering to said mammals a therapeutically effective amount of said vaccine (Claim 23). The de-acetylation is carried out under mild basic conditions, such as 0.01 to 0.5 N NaOH

(Claim 11; page 5, lines 27-31).

Thus, by reading **D4** or **D5**, the skilled person would de-O-acetylate the conjugated polysaccharide Y disclosed in **D3** and thus make a slight constructional change in the conjugated polysaccharide of **D3** which comes within the scope of the customary practice followed by persons skilled in the art, especially as the advantages thus achieved can readily be foreseen in **D4** and **D5**.

Consequently, the subject-matter of independent claims 1, 6, 11, 18-23, 27 and 28 lacks an inventive step (Article 33(3) PCT.

2.2.4 For the same reasons, the dependent claims 2-5, 7-10 and 12-17 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.

2.2.5 **Moreover**, the basic conditions used in the process of document **D3** (2N NaOH: see above) for N-de-acetylation of the capsular polysaccharides from *N. meningitidis*, are much stronger basic conditions than the basic conditions which were used in the process of **D1** or **D2** (0.1-0.2 M NaOH: see above) to remove the O-acetyl groups from the Group Y capsular polysaccharides from *N. meningitidis*, which conditions did not remove the N-acetyl groups from said Group Y capsular polysaccharides.

Thus, although not specifically disclosed in **D3**, the basic conditions employed according to **D3** will remove the O-acetyl groups at the same time as the N-acetyl groups from the Group Y capsular polysaccharides from *N. meningitidis*, and make a conjugate according to claim 1 or 6 of the application.

Therefore, by employing the conditions suggested in the document **D3**, the skilled person would make a conjugate/vaccine according to the application, without the exercise of inventive skill, and the subject-matter of claims 1-28 cannot be considered as involving an inventive step.

2.3 Therefore, the subject-matter of **claims 1-28** can**not** be considered as involving an **inventive** step (Article 33(3) PCT).

3. **Industrial applicability**:

The immunogenic conjugate according to claim 1 or 6 is used in the manufacture of a vaccine (Claims 6 and 18-22).

Thus, the subject-matter of **claims 1-22 and 24-28 complies** with the requirements of Article 33(4) PCT.

4. **Certain observations on the international application**

4.1 All the features of claims 1-5, 10, 14, 15, 17, 23-25, 27 and 28 are not referred to in the description. **Claims 1-5, 10, 14, 15, 17, 23-25, 27 and 28** are therefore **not supported** by the description as required by Article 6 PCT.

4.2 The expressions "polymeric carrier" and "carrier protein" used in **claims 1 and 6** are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT (The description (page 10, lines 1-18) limits and clarifies the meaning of said expressions).

4.3 Attention is drawn to the following: The use of the expression "*incorporated by reference*" (page 8, line 21; page 12, line 7) is not allowed in some designated Contracting States.

4.4 There are obvious spelling mistakes in the application:
Claim 5: "wherin" for "wherein";
Claims 7, 11, 19, 21 and 27: "claim 4" for "claim 6";
Claim 8: "claim 5" for "claim 7";
Claim 9: "claim 6" for "claim 8";
Claims 12, 16, 17, 22 and 23: "claim 9" for "claim 11";
Claim 13: "claim 10" for "claim 12";
Claim 14: "claim 1" for "claim 11";
Claim 15: "claim 12" for "claim 14".